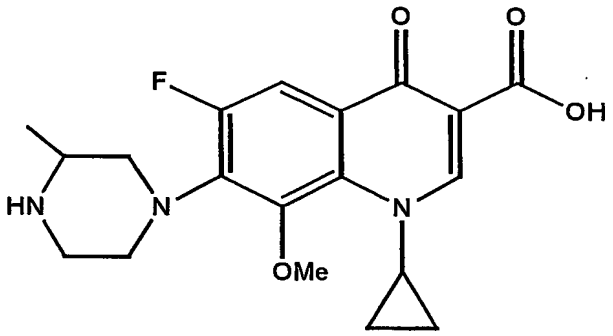
PROCESS FOR PREPARING OMEGA-ANHYDROUS GATIFLOXACIN

FIELD OF THE INVENTION:

The present invention relates to a novel process for the manufacture of omega form of anhydrous Gatifloxacin. Gatifloxacin, chemically known as 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid is represented by the following structural formula (I)



(I)

BACKGROUND OF THE INVENTION

Gatifloxacin is a broad-spectrum quinolone antibacterial agent. US 4,980,470, US 4,997,943, US 5,043,450,and EP 230,295 disclose the preparation of Gatifloxacin. US 5,880,283 and US 6,413,969 disclose twelve different crystalline forms of Gatifloxacin and an anhydrous omega form. However, most of the known processes suffer from the inconvenience of having to employ high temperature heating and column chromatography. In US 4,980,470 and US 5,043,450 Gatifloxacin was purified by adsorbing it in silica-gel column and eluting with chloroform: Methanol: Conc. Aqueous ammonia in the ratio of 20: 6: 1 and then crystallizing it from methanol. These processes are not practical for the large-scale preparations.

US Patent Mo. 4,980,470 discloses the condensation of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid with 2-methylpiperazine in dimethyl sulfoxide. After completion of the reaction, dimethylsulfoxide is removed by distillation under reduced pressure and the residue is purified by silica gel column chromatography. The process as disclosed in above prior art is not practical on commercial scale.

Therefore, there is an urgent need for a novel, inventive and simple process for the preparation and purification of Gatifloxacin, which eventually gives omega form of anhydrous Gatifloxacin.

Objects of the invention:

It is therefore, an important object of the present invention to provide a novel process for the preparation of omega form of anhydrous Gatifloxacin without using high temperature heating and column chromatography..

Another object of the present invention is to provide an economical and plant friendly process for the purification of Gatifloxacin.

SUMMARY OF THE INVENTION:

The above and other objects are achieved by the process of the present invention wherein Gatifloxacin is obtained by crystallization. It has been surprisingly achieved by the addition of suitable organic solvent when reaction complies the condensation stage wherein 2-methylpiperazine reacts with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid, comprising dimethylsulfoxide solvent system. This allows the crystallization of the product, which can be collected by filtration. This provides a significant advantage to the art, which helps avoiding distillation of dimethyl sulfoxide.

During working on purification of Gatifloxacin, it was found that purified material was identical with omega form of anhydrous Gatifloxacin. Prior art references teach preparation of omega form of anhydrous Gatifloxacin by heating hemihydrate or pentahydrate above 170^0C.

The preparation of omega form of anhydrous Gatifloxacin at higher temperature as disclosed in the prior art by heating hemihydrate or pentahydrate, suffers the major disadvantage that there is a possibility of some degradation, which could lead contamination in the product and product so obtained will be difficult to purify.. Hence, the process is unfeasible and uneconomical for a large-scale preparation.

The present invention is based on the surprising finding that such a high temperature of 170^0C is not required for the preparation of omega form of anhydrous Gatifloxacin. The preparation can be accomplished under normal crystallization procedures at relatively lower temperature.

Dissolving in methanol containing potassium hydroxide can purify Gatifloxacin obtained by above procedure. Clear solution thus obtained is adjusted to a pH of 7 to

7.5 by acetic acid resulting in the precipitation of Gatifloxacin. The precipitated Gatifloxacin suspension is then heated to reflux temperature for 30 to 60 minutes.

The product is allowed to cool at ambient temperature, followed by filtration and drying at 70 to 75 ^{0}C for 25-30 hours. The product contains methanol below 500 ppm. as residual solvent. The water content at this stage is less than 2.0%. DSC and X-ray powder diffractogram confirms the nature of the product as omega form of anhydrous Gatifloxacin as disclosed in US 6,413,969. It was found that if the product is dried at a low temperature such as 50-60^{0}C, the residual methanol content in the final product is higher than allowable limits as per ICH guidelines and cannot be removed by drying for a longer period or drying at reduced pressure.

To overcome this problem of high residual methanol content, the dried product is refluxed in either of the following solvent system comprising of (i) methanol, (ii) aqueous methanol (5-10 %), (iii) methanol with 50% removal of solvent at atmospheric pressure or (iv) cyclohexane and dried at 70-75 C for 25-35 hrs to get the residual methanol well within limit as per ICH guidelines.

Gatifloxacin so obtained is suspended in methanol and heated to reflux for 1 hour. Reaction mass is then cooled to 5^{0}C to 10^0 C. The product is collected by filtration and is dried for 35 hours at 70 to 75 ^{0}C. DSC and X-ray powder difractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content upto 500ppm

Gatifloxacin thus obtained with higher residual methanol content is suspended in 5 - 10 % aqueous methanol and refluxed for 1 hour. Reaction mass is then cooled to 5^{0}C to 10^0 C. The product is collected by filtration and is dried for 35 hours at 70 to 75 ^{0}C. Surprisingly hemihydrate or any other hydrated form of Gatifloxacin is not obtained. DSC and X-ray powder diffractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content upto 500ppm.

(1) Gatifloxacin obtained with higher residual methanol content is refluxed with 10 volumes of methanol, 40-60% of methanol is then removed by distillation at atmospheric pressure. The resulting solution is then cooled to 25 to 30^{0}C. The product is collected by filtration and is dried for 24 hours at 70 to 75 ^{0}C. DSC and X-ray powder diffractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content up to 500ppm

(2) Gatifloxacin obtained with higher residual methanol content is refluxed with cyclohexane and methanol along with traces of water is removed by azeotropic distillation using Dean Stark apparatus. The mass is then cooled to 25 to 30 ^{0}C. The product is collected by filtration and is dried for 15 hours at 70 to 75 ^{0}C. DSC and X-ray powder difractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with cyclohexane content 1600 - 1900 ppm and methanol content 5 – 10 ppm.

All the above experiments reproducibly give omega form of anhydrous Gatifloxacin. DSC of all the experiments exhibit a single peak at 191 to 192 ^{0}C with a heating rate of 10 ^{0}C per minute.

The disclosed methods herein have the following advantages over the prior art processes.

1) Avoids column chromatography for purification.
2) Eliminates the heating of the product at very high temperature above melting point.
3) A simple process of heating with methanol which can be performed on commercial scale.
4) Methanol and cyclohexane are recovered and recycled.

DETAILED DESCRITION

The invention will now be described in greater detail with reference to the following preferred embodiment and with reference to the accompanying drawings wherein:

Fig. 1 shows X-Ray powder diffractogram of Gatifloxacin of the present invention, which completely matches with Omega form;

Fig. 2 shows X-ray Powder Diffractogram of this Gatifloxacin Anhydrous of the present invention, which completely matches with omega form of Gatifloxacin

Fig. 3 shows the X-ray powder diffractogram form. of the Gatifloxacin of the present invention as prepared by the process described in Example 3 below which completely matches with Omega form.

Fig. 4 shows the X-ray powder diffractogram form. of the Gatifloxacin of the present invention as prepared by the process described in Example 4 below which completely matches with Omega form.

Fig 5 shows the X-ray powder diffractogram form.of the Gatifloxacin of the present invention as prepared by the process described in Example 5 below which completely matches with Omega form.

Fig. 6 shows the X-ray powder diffractogram form. of the Gatifloxacin of the present invention as prepared by the process described in Example 6 below which completely matches with Omega form.

In the all above figures, the X-ray diffractogram form of the Gatifloxacin as shown in US 6413969 B1 was taken as a standard

In a preferred embodiment, the present invention discloses a process for the manufacture of omega form of anhydrous Gatifloxacin by the following steps.:

a) 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid is reacted with 2-methylpiperazine in DMSO at 60-65°C for 42 (30-40 hrs) hrs.

b) then it is diluted with 1 to 10 volumes preferably 5 volumes of suitable organic solvent as that of DMSO used. The organic solvent used is selected from acetone, acetonitrile, ethyl acetate, isopropyl alcohol and toluene. Isopropyl alcohol is the preferred solvent.

c) the product is collected by filtration or centrifugation, slurried with methanol and is dried for 4 –8 hours at 70-75°C giving crude Gatifloxacin.

d) the product thus obtained is mixed with 3 to 10 volumes, preferably 4 volumes of methanol as that of crude Gatifloxacin and 1 to 2 mole, equivalent preferably 1.2 mole, equivalent of potassium hydroxide resulting in the clear solution which is filtered through hyflow supercell.

e) pH can be adjusted by any organic or inorganic acid t (acetic acid being preferred), resulting in the precipitation of Gatifloxacin.

f) after the pH adjustment the slurry is refluxed for 1 hour.

g) then it is cooled to 25-30° C.

h) the product is collected by filtration, which is dried at 70-75°C for 20-30 hrs, preferably 25-27 hrs. The product thus obtained is identified as omega form of anhydrous.

i) the wet Gatifloxacin (obtained in Example-8 after filteration or centrifugation) is suspended in 5-15 volumes of cyclohexane as that of wet Gatifloxacin, preferably, in 10 volumes of cyclohexane. Reaction mass is refluxed for 3 hrs. During the reflux, methanol & water are removed azeotropically. Reaction mass is than cooled

to 25-30°C followed by filtration and drying at 70-75 C for 12-15 hrs to provide Form-II of Gatifloxacin Anhydrous.

If the product is dried at lower temperature i.e. 50-60^{0}C, the dried product contains high content of methanol as residual solvent than the prescribed limit as per ICH guidelines. In such a case, it is overcome by the following steps:

(A) Gatifloxacin thus obtained is heated at 40 to 70 °C preferably to reflux temperature for 30 to 60 minutes with 5 to 20 volumes preferably 12.5 volume of methanol, the product is filtered at 0 to 25°C; preferably at 5-10°C and is dried at 50 to 100°C for 10 to 50 hrs preferably at 70-75°C for 30-35 hours giving Gatifloxacin having water content 0.24% w/v & methanol content below 500 ppm

(B) Gatifloxacin is heated at 40 to 70 °C, preferably, to reflux temperature with 5 to 20 volume preferably, 12.5 volume of methanol and 0.1 to 10 volume, preferably 1 volume of deionized water and worked up as in method (A) to give a product having water content 0.31% w/w & methanol content = below 500ppm

(C) Gatifloxacin is stirred with 5 to 20 volume preferably 10 volume of methanol. 40 to 60% of methanol is distilled at atmospheric pressure, the product is recovered by filtration at 25 to 30^{0}C is, dried at 70-75°C for 24 hours.

(D) Gatifloxacin is refluxed with 5 to 10 volume of cyclohexane. Methanol and traces of water are removed by azeotropic distillation or by using Dean-Stark apparatus. The product is isolated by filtration at 25 to 30^{0}C and is dried at 70-75°C for 15 hours.

The present invention will now be described with reference to the following non-limiting examples.

Example 1:

Step A:

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid (100g), 2-methylpiperazine (67.8gs) and anhydrous DMSO (300 ml) were stirred for 40-45 hrs at 60-65°C. The reaction mass was then diluted with 1500 ml isopropyl alcohol. It was then stirred for 30 min at 25-30°C followed by cooling at 5 to 10 ^{0}C along with stirring for 2 hours. The product was obtained by filtration, which was washed with 3 x 50 ml isopropyl alcohol followed by drying at 50 to 55°C for 4 hours to provide 71 g Gatifloxacin (Yield 55.9%)

Step B:

100 g Gatifloxacin obtained by the step A disclosed above was purified by dissolving it into solution of 400 ml methanol and 20 g of potassium hydroxide, was filtered through hyflow supercell. The pad was washed with 2 x 20 ml of methanol. The pH of the filtrate was adjusted to 7.0 –7.5 range with acetic acid (20.4 ml). The mixture was then refluxed for 1 hr and was cooled to 25-30°C, and then filtered, giving wash of 2 x 100 ml of methanol. The product was dried at 70-75°C for 20 hrs.

Weight = 80 g. (recovery = 80 %)

Water content = 0.38%

Methanol content = 100ppm

The X-Ray powder diffractogram of this Gatifloxacin completely matches with Omega form (Fig-1)

Example 2:

Step A:

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid (120Kg) 2-methylpiperazine (40.8 Kg), and anhydrous DMSO (361 lit) was heated to 60-65°C temperature and stirred for 2 hrs. A second lot of 2-methylpiperazine (10.2 Kg) was added, and stirred for next 1 hr, at 60-65°C. followed by the addition of a third lot of 2-methylpiperazine (10.2Kg). The mixture was stirred for next 2 hrs at 60-65°C. A fourth lot of 2-methylpiperazine (20.4Kg) was added to the mixture and the stirring was continued for the next 24 hrs maintaining the temperature at 60-65°C followed by cooling to 25-35°C. This reaction mass was added in 1802-l isopropyl alcohol. Reaction mass was then stirred for 30 min at 25-30°C followed by cooling at 5 to 10 ^{0}C along with stirring for 2 hours. Product so obtained was centrifuged, washed with 3 x 60-l isopropyl alcohol. The wet cake of product was mixed with 241-lit methanol and stirred for 1 hr. , Again the product was centrifuged followed by washing with 59 lit of methanol. The wet Gatifloxacin was dried at 60 to 65°C for 6 hrs to yield 81.92 Kg dry Gatifloxacin (Yield= 53.7%)

HPLC Purity = 99.74%

M/C=3.42%

Step B:

The 81.90-g Gatifloxacin obtained by the step disclosed as above was purified by dissolving it into 329 ml Methanol having 16.42 Kg KOH (Pallets) at 25-35°C, within 30 min along with stirring to obtained a clear solution. This solution was filtered through hyflow supercell The hyflow supercell pad was washed with 34 lit of

Methanol. The pH of the filtrate was adjusted to 6.2-7.2 range with acetic acid (17.5 lit) at a temperature of 25-35°C. The mixture was then refluxed for 1 hr and cooled to 25-35°C, stirred for 2 hrs and then centrifuged, washed with 2 x 39.5 lit of methanol. The wet cake was dried in fluid bed drier under following condition to provide a yellowish crystalline Gatifloxacin anhydrous with 70-80 % recovery with water content is less than 2%.

S.No.	Duration	Temperature Range
1.	1 hr	30-35°C
2.	6 hrs	50-60°C
3.	6 hrs	60-65°C
4.	3 hrs	65-70°C
5.	11 hrs	70-75°C

. Weight = 64.2 Kg (recovery =78 %)

The X-ray Powder Diffractogram of this Gatifloxacin Anhydrous completely matches with omega form of Gatifloxacin.

HPLC Purity = 99.95%

Water content = 0.62%

Methanol content = 65 ppm.

The X-ray powder diffractogram. (Fig- 2) of this Gatifloxacin completely matches with Omega form.

Example 3:

40 g of Gatifloxacin (containing methanol as residual solvent more than 5000 ppm) was heated to reflux at 65-70°C for 1 hr with 500-ml methanol. It was then cooled to 5-10°C and was stirred for 1 hr, was filtered and washed with cold methanol (2x20 ml). It was dried at 70-75°C for 35 hrs.

Weight = 37.5 g, (Recovery=93.75%)

Water content = 0.24% w/w.

Methanol content =326 ppm

The X-ray powder diffractogram form. (Fig- 3) of this Gatifloxacin completely matches with Omega form.

Example 4:

40-g Gatifloxacin (containing methanol as residual solvent more than 5000 ppm) is heated to reflux at 65-70°C for 1 hr with 500-ml methanol and 40 ml deionized

water. Then it was cooled to 5-10°C and the temperature was maintained for 1 hr, filtered, washed with cold methanol (2x20 ml), was dried at 70-75°C for 35 hrs.

Weight = 38 g, (Recovery=95%)

Water content = 0.31% w/w

Methanol content =421 ppm.

The X-ray powder diffractogram (Fig. 4) of this Gatifloxacin completely matches with Omega form.

Example 5

20 g Gatifloxacin (containing methanol as residual solvent more than 5000 ppm.) is stirred with 200 ml of methanol. 100 ml of methanol was distilled out at atmospheric pressure. It was cooled to 25-30°C and filtered, gave wash of methanol (2x10 ml) and dried at 70-75°C for 24 hrs.

Weight = 19 g, (Recovery 95%)

Water content = 0.38% w/w.

Methanol content =449 ppm

The X-ray powder diffractogram. (Fig-5) of this Gatifloxacin completely matches with Omega form.

Example 6:

(A) <u>Preparation of Omega form of Gatifloxacin Anhydrous:</u>

17 g Gatifloxacin (Obtained from Example-2 & containing methanol as residual solvent more than 5000 ppm.) was dried by suspending it into 170 ml of cyclohexane. The suspension was refluxed and methanol along with traces of water was removed azeotropically by dean stark apparatus. The reaction mass was cooled to 25-30°C and filtered, dried at 70-75°C for 15 hrs. Weight = 15.8 g, (Recovery = 92.9%)

Water content = 0.38% w/w.

Methanol content = 50 ppm

The X-Ray powder diffractogram of this Gatifloxacin completely matches with Omega form . (Fig-6)

The X-ray powder diffractogram of the Gatifloxacin was also compared with that disclosed in WO 03/086402. It matches completely matches with form-II of anhydrous Gatifloxacin as disclosed in WO 03/086402, which is incorporated herein by reference

Omega Form :

WO 03/086402 Omega Form		Omega Form prepared herein this patent	
2θ (°)	Intensity	2θ (°)	Intensity
7.763	100	7.760	45
19.722	100	19.740	100
13.615	89.3	13.610	70
25.927	71.9	25.940	42
12.854	71.7	12.850	37
28.650	40.9	28.650	24
20.491	35.2	20.510	37
14.112	29.3	14.140	30
10.196	26.8	10.230	26
23.593	15.1	--------	---
23.765	14.9	23.790	25
16.333	12.2	16.370	14
27.558	10.9	27.580	11
14.932	9.8	14.970	17
21.456	9.7	21.460	12
30.496	8.4	30.440	11
17.013	7.2	17.030	12
30.872	6.7	30.890	11
31.477	5.6	31.480	7
24.440	3.7	24.460	12